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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,014	10/03/2003	David V. Goeddel	P0960R1D1C3	8921

23552 7590 09/06/2007
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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
09/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/679,014	**Applicant(s)** GOEDDEL ET AL.	
	Examiner Agnieszka Boesen	**Art Unit** 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *4/19/2004 and 4/19/2005*.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Applicants' response filed on June 19, 2006 is acknowledged. Applicant's amendment filed October 16, 2006 and sequence listing filed October 16, 2006 and June 18, 2007 are acknowledged. Claims 1-37 have been canceled. New claims 39-46 have been added. Claims 38-46 are pending and under examination.

Election/Restrictions

Applicant's election of group VIII, claim 38 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

Acknowledgment is made for priority to a CON application 09/579,933, which is a CON of application 09/459,952, which is CON of application 09/020,467, which is US Patent 6,060,303, which is a DIV of application 08/700,749, which is US Patent 5,789,550, which claims priority to 60/002,382.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on April 19, 2004 and April 19, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites, "(...) wherein the cell is an Epstein-Barr virus associated tumor cell." The recitation of a phrase "associated" renders the claim indefinite because the skilled artisan would not know what type of association is required between the cell and the Epstein-Barr virus (EBV). It is not clear if the recited association refers to a cell infected with the Epstein-Barr virus, a cell that carries EBV genes in its genome without comprising actively replicating EBV particles, a cell transformed with EBV or other type of association. The present specification does not provide a definition clarifying the claimed association and what it encompasses. The skilled artisan would be unable to determine the metes and bounds of the present claim. Clarification and correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn a method of modulating TRAF mediated signal transduction in a cell comprising introducing into said cell a nucleic acid encoding I-TRAF polypeptide, a polypeptide having at least 70% sequence identity with the TRAF binding domain of a native sequence I-TRAF polypeptide and capable of inhibiting a TRAF-mediated signaling event, as well as fragments of the said polypeptides.

The present specification does not provide an adequate written description for the claimed methods, particularly with respect to 1) the claimed polypeptides having 70% sequence identity with the TRAF binding domain of native I-TRAF polypeptide, 2) the fragments of native I-TRAF polypeptide and the fragments of polypeptides having 70% sequence identity with the TRAF binding domain of native I-TRAF polypeptide, 3) the truncated murine I-TRAF –alpha polypeptide, 4) the equivalent part of a human I-TRAF sequence, 5) the TRAF2 binding fragments, 6) polypeptides having at least 70% sequence identity with SEQ ID NO: 5, and 7) the conditions suitable for expression of the I-TRAF polypeptide from the nucleic acid molecule.

The claimed compounds have not been sufficiently described in terms of their structure and function. The claims refer to a function such as: capable of inhibiting a TRAF mediated signaling event resulting in modulation of TRAF mediated signal transduction. Based solely on the knowledge of the required protein function and without specific guidance with respect to the sequences of the claimed genus of protein fragments, the skilled artisan would be unable to decipher which particular sequences would have the claimed function. Claiming a product based on function does not provide sufficient description of the product as claimed. With regard to the conditions suitable for expression of the I-TRAF polypeptide from the nucleic acid molecule, the specification does not identify the specific reaction conditions with regard to chemical and biochemical components of the claimed conditions. Applicant is required to point out where in the specification the claimed suitable conditions are described.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The Applicant has not described which part of the native I-TRAF polypeptide should be conserved in order to maintain the capability to inhibit or modulate the TRAF mediated signaling.

It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. It is known in the art that the substitution of some amino acids within the protein sequence may cause the loss of function of the protein. Thus, the large number of sequences encompassed by the current claims may or may not be effective in modulating the TRAF mediated signal transduction. See the following publications that support this unpredictability (Baker et al., Protein Structure Predication and Structural Genomics, Science (2001) Vol. 294, No. 5540, pages 93- 96; Attwood, T. The Babel of Bioinformatics, Science (2000) Vol. 290, no. 5491, pages 471-473).

The skilled artisan cannot envision the detailed structure of a genus of compounds that are contemplated in the invention. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 38-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make, and/or use the invention.

Claims are drawn a method of modulating TRAF mediated signal transduction in a cell comprising introducing into said cell a nucleic acid encoding I-TRAF polypeptide, a polypeptide having at least 70% sequence identity with the TRAF binding domain of a native sequence I-TRAF polypeptide and capable of inhibiting a TRAF-mediated signaling event, as well as fragments of the said polypeptides. The claims are rejected because Applicant's specification lacks sufficient enablement to support the full scope of the claimed invention. In particular there is lack of sufficient enablement to support 1) the claimed methods encompassing *in vivo* modulation of TRAF mediated signal transduction, 2) the *in vitro* and *in vivo* methods of modulating TRAF mediated signal transduction, wherein modulation is activation of TRAF signaling, 3) the *in vitro* and *in vivo* methods of modulating TRAF mediated signal transduction comprising introducing into a cell a large genus of polypeptides that encompass fragments and truncations of I-TRAF, and 4) the methods of modulating TRAF mediated signal transduction in all known cells.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors deemed relevant are those of the amount of direction and the working examples provided, the quantity of experimentation necessary, the (un)predictability of the art, and the breadth of the claims.

The present claims are interpreted to encompass both the *in vitro* and *in vivo* methods of modulating TRAF mediated signal transduction. The claims broadly encompass a method of modulating TRAF mediated signal transduction in an unspecified broadly claimed cell type, which is interpreted to encompass all known cells. The recitation of "a method of modulation" is broadly interpreted to encompass both positive and negative modulation, including inhibition and activation of TRAF mediated signal transduction. The claimed method is drawn to modulating TRAF mediated signal transduction comprising introduction into a cell a large genus of polypeptides that encompass fragments and truncations of I-TRAF.

The nature of the present invention concerns a method for modulating TRAF-mediated signal transduction in a cell comprising introducing into a cell a nucleic acid encoding TRAF inhibitor (I-TRAF). **TRAF** has been identified as a tumor necrosis factor receptor associated protein that transduces signals from TNF receptor 2, CD40, and is required for CD40 and TNF-mediated activation of transcription factor NF-kB. **I-TRAF** has been identified as TRAF-interacting protein that regulates TRAF-mediated signal transduction. Rothe et al. (PNAS, 1996, Vol. 93, p. 8241-8246, in IDS of April 19, 2004) have shown that overexpression of I-TRAF inhibits TRAF2-mediated NF-kB activation signaled by CD40 and TNF alpha receptors. The nature of the present invention concerns the TRAF proteins that interact with the C-terminal cytoplasmic domain of Epstein-Barr virus (EBV) and transform a dominant oncogene LMP1 that activates transcription factor NF-kB, which induces up- regulation of B cell activation markers and cell growth.

Devergne et al. (Journal of Virology, 1998, Vol. 72, p. 7900-7908) has shown that signaling trough TRAF2 and TRAF5 is important for the effects of LMP1 (an EBV latent membrane protein, a dominant oncogene) on epithelial cell growth including effects on early lesions of nasopharyngeal carcinoma. Davergne et al. discusses that LMP1 stimulates TRAF1 expression that contributes to NF-kB activation, which plays an important role in antiapoptotic and transforming effects of LMP1. Kehry (Journal of Immunology, 1996, Vol. 156, p. 2345-2348) teaches that TRAF proteins associate with cytoplasmic tail of CD40, and that the CD40 receptor is expressed on antigen presenting cells, follicular dendritic cells, dendritic cells, macrophages, thymic epithelial cells, hematopoetic progenitors and some carcinoma cells.

As discussed above the claims are broadly drawn to a method of modulating TRAF mediated signal transduction in a cell. The specification contemplates treating a tumor associated with EBV virus comprising administering to a patient a TRAF inhibitor. The present claims broadly encompass the contemplated *in vivo* methods. The Examples in the specification provide guidance with respect to inhibitory effects of I-TRAF on TRAF2 and TNF-R2, and on activation of NF-kB in human embryonic kidney 293 cells (see [0118] and [0120]). Thus the current Examples provide evidence that I-TRAF has the capability to inhibit TRAF2 association with TNF-R2, and activation of NF-kB in the *in vitro* setting. However, the guidance provided in the current specification does not enable the skilled artisan to practice the current method in an *in vivo* setting in an animal.

Further, the guidance provided in the current specification does not enable the skilled artisan to practice the current method wherein the claimed modulation encompasses activation of TRAF mediated signal transduction. Additionally, the present specification does not provide an adequate enablement to allow the skilled artisan to practice the present method in all cell types. Based on the teaching of Kehry, as discussed above, because TRAF associates with CD40 that is present in antigen presenting cells and some carcinoma cells, the skilled artisan would not consider modulating TRAF mediated signaling in cells that do not express TRAF molecules. Moreover, the skilled artisan would require to conduct an undue amount of experimentation to practice the present method using all available cells that do express TRAF molecule. The skilled artisan would not intend to module TRAF mediated signal transduction in normal (non-cancerous) cells. The specification does not provide guidance with respect to how would the artisan spare modulation of TRAF signaling in normal cells. The art does not provide teachings showing that TRAF mediated cell signaling could be inhibited *in vivo* or in primary cancer cells *in vitro*. The inhibition of TRAF mediated signaling has been only shown in transformed cells lines such as in human embryonic kidney 293 cells as evidenced by Rothe et al. (PNAS, 1996, Vol. 93, p. 8241-8246). Furthermore the specification does not provide an adequate enablement to allow the skilled artisan to practice the current method comprising introducing into a cell a large genus of polypeptides that encompass fragments and truncations of I-TRAF and thereby modulating TRAF mediated signaling.

Thus considering the guidance in the present specification that is limited to practicing the present methods in the *in vitro* setting, wherein the claimed modulation is inhibition of TRAF mediated signal transduction comprising introducing a nucleic acid encoding I-TRAF polypeptide into human embryonic kidney 293 cells, in conjunction with the nature of the invention and the state of the prior art, it would require an undue amount of experimentation to practice the present method in the full scope as claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday between 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AB

Agnieszka Boesen, Ph.D.

/Stacy B. Chen/ 8-29-2007
Primary Examiner, TC1600